CLAIMS

What is claimed is:

1. A method of isolating islets from a pancreas wherein a process variable describing the chemical character of the islet processing solution is the process temperature (T) and the process variable is controlled via a setpoint and the process temperature setpoint is between 4.0 degrees Celsius and 44.0 degrees Celsius.

2. The method of claim 1 wherein the process controller is a PID (proportional, integral, derivative) controller and the process temperature setpoint is between 4.0 degrees Celsius and 44.0 degrees Celsius.

3. The method of claim 1 wherein the process controller is a microprocessor temperature controller and the process temperature setpoint is between 4.0 degrees Celsius and 44.0 degrees Celsius.

4. The method of claim 1 wherein the process controller is a microprocessor controller and the process temperature setpoint is between 4.0 degrees Celsius and 44.0 degrees Celsius.

5. The method of claim 1 wherein the process controller is a microprocessor computer and the process temperature setpoint is between 4.0 degrees Celsius and 44.0 degrees Celsius.

6. The method of claim 1 wherein the process controller is a variable resistance transformer and the process temperature setpoint is between 4.0 degrees Celsius and 44.0 degrees Celsius.

7. The method of claim 1 wherein the process temperature is generated by an electrical resistance element and the process temperature setpoint is between 4.0 degrees Celsius and 44.0 degrees Celsius.

8. The method of claim 1 wherein the process temperature is generated by steam and the process temperature setpoint is between 4.0 degrees Celsius and 44.0 degrees Celsius.

9. The method of claim 1 wherein the process temperature is generated by a recirculating fluid bath and the process temperature setpoint is between 4.0 degrees Celsius and 44.0 degrees Celsius.

10. The method of claim 1 wherein the process temperature is generated by the temperature of the ambient surrounding and the process temperature setpoint is between 4.0 degrees Celsius and 44.0 degrees Celsius.

11. The method of claim 1 wherein the process variable is the process percent hydrogen (pH) concentration and the process controller is a microprocessor pH controller and the process percent hydrogen concentration setpoint is between pH 6.00 and pH 8.00.

12. The method of claim 1 wherein the process variable is the process percent hydrogen (pH) concentration and the process controller is a microprocessor controller and the process percent hydrogen concentration setpoint is between pH 6.00 and pH 8.00.

13. The method of claim 1 wherein the process variable is the process percent hydrogen (pH) concentration and the process controller is a microprocessor computer and the process percent hydrogen concentration setpoint is between pH 6.00 and pH 8.00.

14. The method of claim 1 wherein the process variable is the process percent hydrogen (pH) concentration and the process percent hydrogen concentration is controlled by the addition of an acid or base to the process solution thereby buffering the process percent hydrogen concentration in the process solution between pH 6.00 and pH 8.00.

15. The method of claim 1 wherein the process variable is the process flowrate (F) and the process controller is a microprocessor flow controller and the process flowrate setpoint is between 10.0 milliliters per minute (10.0 ml/min) and 4000.0 milliliters per minute (4000.0 ml/min).

16. The method of claim 1 wherein the process variable is the process flowrate (F) and the process controller is a microprocessor controller and the process flowrate setpoint is between 10.0 milliliters per minute (10.0 ml/min) and 4000.0 milliliters per minute (4000.0 ml/min).

17. The method of claim 1 wherein the process variable is the process flowrate (F) and the process controller is a microprocessor computer and the process flowrate setpoint is between 10.0 milliliters per minute (10.0 ml/min) and 4000.0 milliliters per minute (4000.0 ml/min).

18. The method of claim 1 wherein the process variable is the process dissolved oxygen (DO) concentration and the process controller is a microprocessor DO controller and the process dissolved oxygen concentration setpoint is between 0.000000001 milligrams per milliliter (0.000000001mg/ml) DO and 2.0 milligrams per milliliter (2.0 mg/ml) DO.

19. The method of claim 1 wherein the process variable is the process dissolved oxygen (DO) concentration and the process controller is a microprocessor controller and the process dissolved oxygen concentration setpoint is between 0.000000001 milligrams per milliliter (0.000000001mg/ml) DO and 2.0 milligrams per milliliter (2.0 mg/ml) DO.

20. The method of claim 1 wherein the process variable is the process dissolved oxygen (DO) concentration and the process controller is a microprocessor computer and the process dissolved oxygen concentration setpoint is between 0.000000001 milligrams per milliliter (0.000000001mg/ml) DO and 2.0 milligrams per milliliter (2.0 mg/ml) DO.

21. The method of claim 1 wherein the process variable is the process dissolved oxygen (DO) concentration and the process dissolved oxygen concentration is controlled by sparging the process solution with an inert gas either helium, or neon, or argon, or krypton, or xenon thereby displacing dissolved oxygen from the process solution.

22. The method of claim 1 wherein the process variable is the process dissolved nitric oxide (NO) concentration and the process controller is a microprocessor NO controller and the process dissolved nitric oxide concentration setpoint is between 0.00000000000001 moles per liter (0.01 picomoles/liter) NO and 0.01 mole per liter (0.01 mol/liter) NO.

23. The method of claim 1 wherein the process variable is the process dissolved nitric oxide (NO) concentration and the process controller is a microprocessor controller and the process dissolved nitric oxide concentration setpoint is between 0.00000000000001 moles per liter (0.01 picomoles/liter) NO and 0.01 mole per liter (0.01 mol/liter) NO.

24. The method of claim 1 wherein the process variable is the process dissolved nitric oxide (NO) concentration and the process controller is a microprocessor computer and the process dissolved nitric oxide concentration setpoint is between 0.00000000000001 moles per liter (0.01 picomoles/liter) NO and 0.01 mole per liter (0.01 mol/liter) NO.

25. The method of claim 1 wherein the process variable is the process dissolved nitric oxide (NO) concentration and the process dissolved nitric oxide concentration is controlled by sparging the process solution with an inert gas either helium, or neon, or argon, or krypton, or xenon displacing dissolved oxygen from the process solution thereby inhibiting nitric oxide in the process solution.

26. The method of claim 1 wherein the process variable is the process endotoxin (E) concentration and the process controller is a microprocessor E controller and the process endotoxin concentration setpoint is between 0.000000001 endotoxin units (EU) per milligram (1.0 nanoEU/mg) and 100.0 endotoxin units per milligram (100.0 EU/mg).

27. The method of claim 1 wherein the process variable is the process endotoxin (E) concentration and the process controller is a microprocessor controller and the process endotoxin concentration setpoint is between 0.000000001 endotoxin units (EU) per milligram (1.0 nanoEU/mg) and 100.0 endotoxin units per milligram (100.0 EU/mg).

28. The method of claim 1 wherein the process variable is the process endotoxin (E) concentration and the process controller is a microprocessor computer and the process endotoxin

concentration setpoint is between 0.000000001 endotoxin units (EU) per milligram (1.0 nanoEU/mg) and 100.0 endotoxin units per milligram (100.0 EU/mg).

29. The method of claim 1 wherein the process variable is the process endotoxin (E) concentration and the process endotoxin concentration is controlled by the addition of endotoxin neutralizing protein (ENP) to the process solution thereby neutralizing endotoxin in the process solution.

30. The method of claim 1 wherein the process variable is the process endotoxin neutralizing protein (ENP) concentration and the process controller is a microprocessor ENP controller and the process endotoxin neutralizing protein concentration setpoint is between 0.00000000000001 moles per liter (0.01 picomoles/liter) ENP and 0.01 moles per liter (0.01 mol/liter) ENP.

31. The method claim 1 wherein the process variable is the process proteolytic enzyme [PE] activity (measured by the process metalloendoproteinase [collagenase] concentration) and the process proteolytic enzyme activity of collagenase classes I and II is controlled by the addition of antibiotics, either tetracycline, or minocycline, or doxycycline to the process solution thereby neutralizing metalloendoproteinase (collegenase) in the process solution.

32. The method claim 1 wherein the process variable is the process proteolytic enzyme [PE] activity (measured by the process metalloendoproteinase [collagenase] concentration) and the process proteolytic enzyme activity of collagenase classes I and II is controlled by the addition of chelators of divalent cations, either citrate, or EDTA, or EGTA to the process solution thereby neutralizing metalloendoproteinase (collagenase) in the process solution.

33. The method claim 1 wherein the process variable is the process proteolytic enzyme [PE] activity (measured by the process metalloendoproteinase [collagenase] concentration) and the process proteolytic enzyme activity of collagenase classes I and II is controlled by the addition of amino acids either cysteine or cystine to the process solution thereby neutralizing metalloendoproteinase (collegenase) in the process solution.

34. The method of claim 1 wherein the process variable is the process proteolytic enzyme [PE] activity and the process controller is a microprocessor proteolytic enzyme neutralization (PEN) controller and the (process proteolytic enzyme [PE] activity measured by the metalloendoproteinase [collagenase] concentration) process metalloendoproteinase (collagenase) setpoint is between 0.00000000000001 moles per liter (0.01 picomoles/liter) and 0.01 moles per liter (0.01 mol/liter).

metalloendoproteinase [collagenase] concentration) process metalloendoproteinase (collagenase) setpoint is between 0.00000000000001 moles per liter (0.01 picomoles/liter) and 0.01 moles per liter (0.01 mol/liter).

36. The method of claim 1 wherein the process variable is the process antibiotic (A) concentration and the process controller is a microprocessor proteolytic enzyme neutralization (PEN) controller and the process antibiotic concentration setpoint is between 0.00000000000001 moles per liter (0.01 picomoles/liter) A and 0.01 mole per liter (0.01 mol/liter) A.

37. The method of claim 1 wherein the process variable is the process nitric oxide synthase (NOS) concentration and the process nitric oxide synthase concentration is controlled by the addition of derivatives of L-arginine either aminoguanidinie, or N, N'-diaminoguanidine, or methylguanidine, or 1, 1-dimethylguanidine to the process solution thereby inhibiting nitric oxide synthase in the process solution.

38. The method of claim 1 wherein the process variable is the process nitric oxide synthase (NOS) concentration and the process nitric oxide synthase concentration is controlled by the addition of 2,4-diamino-6-hydroxy-pyrimidine to the process solution thereby inhibiting nitric oxide synthase in the process solution.

39. The method of claim 1 wherein the process variable is the process solution pressure (P) and the process solution pressure setpoint is between 5.0 pounds per square inch gauge (psig) pressure and 150.0 pounds per square gauge (psig) pressure.

40. The method of claim 1 wherein the process variable is the process carbon dioxide (CO2) concentration and the process dissolved carbon dioxide concentration is controlled by sparging the process solution with an inert gas either helium, or neon, or argon, or krypton, or xenon displacing dissolved carbon dioxide from the process solution.

41. The method of claim 1 wherein the pancreas is a human pancreas.

42. The method of claim 1 wherein the pancreas is a transgenic porcine pancreas.

43. The method of claim 1 wherein the pancreas is a non-transgenic porcine pancreas.

44. The method of claim 1 wherein the pancreas is a transgenic mammalian pancreas.

45. The method of claim 1 wherein the pancreas is a non-transgenic mammalian pancreas.

46. The method of claim 1 wherein the pancreas is a transgenic fish pancreas.

47. A method of isolating islets from a pancreas incorporating a system, the system composed of an apparatus for processing a pancreas in physiologic process solution comprising;

a plurality of process solution pumps separate from the apparatus composed of a process flow

(F) pump, endotoxin neutralizing protein (ENP) pump, proteolytic enzyme neutralizing (ENP) pump, acid pump, and base pump, connected to process solution tubing placed in a fixed position on the apparatus;

a plurality of electromechanical solenoid process valves placed in fixed positions on the apparatus connected to process tubing placed in a fixed position on the apparatus;

a plurality of process heaters and process heat exchangers placed in a fixed positions on the apparatus;

a plurality of gas tanks, gas regulators, and gas valves composed of an oxygen tank, oxygen gas regulator, inert gas tank, inert gas regulator, and inert gas valve, separate from the apparatus connected by process tubing placed in fixed positions on the apparatus;

a dynamic flow tissue digestion chamber placed in a movable position on the apparatus connected to a process pump separate from the apparatus and process tubing placed in a fixed position on the apparatus;

a plurality of electrical (electronic) analog and digital process sensors placed in fixed positions on the apparatus composed of temperature (thermocouple) sensors, percent hydrogen (pH) sensor, dissolved oxygen (DO) sensor, dissolved nitric oxide (NO) sensor, endotoxin (E) sensor, carbon dioxide (CO2) sensor, and pressure transducer (P) sensor;

a plurality of microprocessor process controllers separate from the apparatus accepting electrical (electronic) input signals (feedback) from process sensors on the apparatus generating electrical (electronic) output signals (feedback) to process pumps, process heaters, process heat exchangers, and dynamic flow tissue digestion chamber process valves composed of a temperature (T) controller, percent hydrogen (pH) controller, dissolved oxygen (DO) controller, dissolved nitric oxide (NO) controller, endotoxin neutralizing protein (ENP) controller, and proteolytic enzyme neutralizing (ENP) controller;

a microprocessor computer consisting of a keyboard, a pointing device (mouse), a graphical display (computer monitor), a hard drive (HD), random access memory (RAM), read only memory (ROM), erasable programmable read only memory (EPROM), and software program code separate from the apparatus accepting electrical (electronic) input signals (feedback) from process sensors on the apparatus and microprocessor processor controllers separate from the apparatus generating electrical (electronic) output signals

(feedback) to process pumps, process heaters, process heat exchangers, dynamic flow tissue digestion chamber, and process valves;

wherein the process sensors, process pumps, process valves, dynamic flow tissue digestion chamber, microprocessor process controllers, and microprocessor computer are electrically (electronically) interconnected with an analog and digital electrical (electronic) interface and islet isolation proceeds methodically while the system operates via process setpoints.

48. The method of claim 47 wherein islet isolation proceeds automatically.

49. The method of claim 47 wherein real time electrical (electronic) process data describing the chemical character of the islet processing solution during islet isolation is acquired and automatically recorded to a data file via data acquisition (DAQ) concurrent with islet isolation.

50. The method of claim 47 wherein the pancreas is a human pancreas.

51. The method of claim 47 wherein the pancreas is a transgenic porcine pancreas.

52. The method of claim 47 wherein the pancreas is a non-transgenic porcine pancreas.

53. The method of claim 47 wherein the pancreas is a transgenic mammalian pancreas.

54. The method of claim 47 wherein the pancreas is a non-transgenic mammalian pancreas.

55. The method of claim 47 wherein the pancreas is a transgenic fish pancreas.

56. A method of isolating islets from a pancreas incorporating a system, the system composed of an apparatus for processing a pancreas in physiologic process solution comprising;

a dynamic flow tissue digestion chamber incorporating internal baffles enhancing mechanical disruption of the pancreas;

a dynamic flow tissue digestion chamber incorporating alternating forward and reverse process solution flow through the chamber providing forced convective cooling to the pancreas;

an electric servomotor in a fixed position on the apparatus providing alternating forward and reverse rotary motion to the dynamic flow tissue digestion chamber enhancing mechanical disruption of the pancreas;

a duality of electrical slip ring bearing connectors placed in a fixed position at either end of the dynamic flow tissue digestion chamber allowing electrical signal transmission through the electrical slip rings concurrent with rotary motion;

a plurality of self contained sonic transducers separate from the apparatus placed in fixed positions around the dynamic flow tissue digestion chamber;

a microprocessor frequency controller separate from the apparatus generating electrical

(electronic) output signals (feedback) through the electrical slip rings to the sonic transducers located on the dynamic flow tissue digestion chamber;

wherein the dynamic flow tissue digestion chamber, the electrical slip rings, microprocessor frequency controller, and sonic transducers are electrically (electronically) interconnected and islet isolation proceeds methodically via a process setpoint.

57. The method of claim 56 wherein islet isolation proceeds automatically.

58. The method of claim 56 wherein the internal volume of the dynamic flow tissue digestion chamber is approximately 500.0 milliliters (500.0 ml).

59. The method of claim 56 wherein the dynamic flow tissue digestion chamber is operated between 5.0 rotations per minute (5.0 rpm) and 500.0 rotations per minute (500.0 rpm).

60. The method of claim 56 wherein the sonic transducers discontinuously transmit discrete pulsed frequencies between 2.0 kilohertz (2.0 khz) and 200.0 kilohertz (200.0 khz).

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